IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: ZOLOFT (SERTRALINE HYDROCLORIDE) PRODUCTS LIABILITY LITIGATION	**MDL No. 2342** **12-md-2342**
THIS DOCUMENT APPLIES TO: ***ALL ACTIONS***	

MEMORANDUM OPINION

Rufe, J. **January 23, 2015**

Before the Court is the Plaintiff's Steering Committee's ("PSC's") Motion for Partial Reconsideration of the Court's Memorandum Opinion and Order dated June 27, 2014 ("Opinion"). For the reasons set forth below, the Motion will be denied. The discussion that follows assumes familiarity with the earlier Opinion.

I. BACKGROUND

The PSC produced to Defendants ("Pfizer") an expert report on general causation prepared by Dr. Anick Bérard. Pfizer filed a motion to exclude Dr. Bérard's expert testimony. This matter was fully briefed and a several-day hearing was held, after which the Court issued its opinion and granted Pfizer's motion. The opinion set forth a detailed and multi-faceted rationale for finding Dr. Bérard's testimony unreliable, including her inattention to the principles of replication and statistical significance, her use of certain principles and methods without demonstrating either that they are recognized by her scientific community or that they should otherwise be considered scientifically valid, the unreliability of conclusions drawn without adequate hypothesis testing, the unreliability of opinions supported by a "cherry-picked" sub-set

of research selected because it was supportive of her opinions (without adequately addressing non-supportive findings), and Dr. Bérard's failure to reconcile her currently expressed opinions with her prior opinions and her published, peer-reviewed research. Taking into account all these factors, as well as others discussed in the Opinion, the Court found that Dr. Bérard departed from well-established epidemiological principles and methods, and that her opinion on human causation must be excluded. The PSC then timely filed its motion for partial reconsideration.

II. STANDARD OF REVIEW

A motion for reconsideration "is extremely limited. Such motions are not to be used as an opportunity to relitigate the case; rather, they may be used only to correct manifest errors of law or fact or to present newly discovered evidence."[1] The Third Circuit has held that "a judgment may be altered or amended if the party seeking reconsideration shows at least one of the following grounds: (1) an intervening change in the controlling law; (2) the availability of new evidence that was not available when the court granted the motion [to be reconsidered]; or (3) the need to correct a clear error of law or fact or to prevent manifest injustice."[2]

III. DISCUSSION

The PSC's motion argues that the Court made a clear error of law which must be corrected to prevent manifest injustice. Specifically, the PSC argues that the Supreme Court's reasoning in *Matrixx Initiatives, Inc. v. Siracusano*,[3] and the Third Circuit's ruling in *DeLuca v. Merrell Dow Pharmaceuticals, Inc.*,[4] do not permit the Court to apply a bright-line rule and exclude a general causation expert for drawing conclusions about causation in the absence of

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[1] *Blystone v. Horn*, 664 F.3d 397, 415 (3d Cir. 2011); *see also Howard Hess Dental Labs. Inc. v. Dentsply Int'l, Inc.*, 602 F.3d 237, 251 (3d Cir. 2010); *Harsco Corp. v. Zlotnicki*, 779 F.2d 906, 909 (3d Cir. 1985).

[2] *Max's Seafood Cafe ex rel. Lou-Ann, Inc. v. Quinteros*, 176 F.3d 669, 677 (3d Cir. 1999).

[3] 131 S. Ct. 1309 (2011).

[4] 911 F.2d 941 (3d Cir. 1990).

replicated, statistically significant associations.

Contrary to the PSC's contention, the Court did not hold that there is a "legal requirement of repeated or replicated statistically significant epidemiological findings in order to establish general causation,"[5] nor did it rely on any such holding made by another court. Rather, the Court set forth its factual finding that *epidemiologists*, such as Dr. Bérard, who are examining potential teratogens generally will not draw causal conclusions in the absence of replicated statistically significant epidemiological findings and application of the Bradford-Hill criteria.[6] In discussing these criteria, the Court was describing a scientific methodology, not setting forth a legal standard. The Court made this factual finding after review of the published literature relied upon by Dr. Bérard and other experts, as well as its review of the reports and testimony of both parties.[7] The PSC argues that the Court's citation to similar language in *Wade-Greaux v. Whitehall Laboratories, Inc.*[8] indicates that the Court misconstrued a factual finding of that court as a legal conclusion. The Court did not; it cited *Wade-Greaux* only to demonstrate that other courts have made similar findings regarding the prevailing standards for scientists in Dr. Bérard's field.[9]

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[5] Pl. Reply Brief at 6.

[6] As the court pointed out in *In re Diet Drugs*, medical experts, and especially physicians opining as to specific rather than general causation, may rely on data other than statistical evidence from epidemiological studies, such as a differential diagnosis, which is a "technique generally accepted in the medical community." *In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Products Liab. Litig.*, 890 F. Supp. 2d 552, 561 (E.D. Pa. 2012) (citing *Heller v. Shaw Industries, Inc.*, 167 F. 3d 146, 155 (3d Cir. 1999)). However, Dr. Bérard is an epidemiologist, not a physician, and the Court has evaluated the reliability of her methods accordingly. Moreover, the Court notes that, unlike the association at issue in *In re Diet Drugs*, which had not been the subject of any epidemiological study, the use of Zoloft during pregnancy has been the subject of many large epidemiological studies designed with the goal of identifying any associations between maternal SSRI /Zoloft use and a broad range of birth defects. Even so, the Court has evaluated Dr. Bérard's methods according to the *Daubert* principles, and did not apply any bright-line exclusionary rules to her causation analysis.

[7] See June 27, 2014 Opinion at 9, 10-11, 19-21.

[8] 874 F. Supp. 1441, 1453 (D.V.I. 1994), *aff'd* 46 F.3d 1120 (3d Cir. 1994).

[9] *Id.* In its unpublished opinion, the Third Circuit affirmed the district court's decision to exclude the expert testimony in *Wade-Greaux*, finding that the district court correctly applied the relevant legal principles, expressly agreeing with the district court's conclusions, finding no abuse of discretion, and finding no reason "to repeat what

Moreover, the Court did not hold, as a matter of law, that any causation expert must be excluded under *Daubert* in the absence of replicated, statistically significant findings, nor did the Court exclude Dr. Bérard's testimony solely based upon her failure to support her opinions with replicated, statistically significant findings. The Court considered statistical significance to be one important indicator of reliable methodology, but did not hold that this factor "mechanically control[s] whether an epidemiological analysis is sufficiently reliable to be admissible."[10] The Court found that Dr. Bérard's method of examining trends in odds ratios and confidence intervals without regard to statistical significance and without further statistical analysis was not of "uncontroverted validity" in her field of epidemiology, and, given this finding, the Court further assessed the validity of Dr. Bérard's method (the "Rothman approach"), applying the *Daubert* standard.[11]

This Court also examined Dr. Bérard's methodology with regard to her analysis of the Bradford-Hill criteria, which the PSC acknowledged to be well-established causation criteria used by epidemiologists. The Court expressly found that strength of association (of which statistical significance is a measure) and replication are but two of the Bradford-Hill criteria for inferring causation, and considered the reliability of Dr. Bérard's methodology with regard to *all*

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the district court exhaustively explained." *Wade-Greaux v. Whitehall Labs., Inc.*, No. 94-7199, Memorandum Opinion at 2 (3d Cir. Dec. 15, 1994). As a further example, in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S.579, 593 (1993), another case in which it was claimed that a medication had a teratogenic effect when used during pregnancy, the Supreme Court wrote that the hallmarks of the scientific method are formulation of hypotheses, hypothesis testing through experimentation, and attempting to falsify the hypothesis. The last means that a scientist attempts to rule out the possibility that any relationship or association between variables of interest is due to background risk or chance alone. Although the Supreme Court did not say as much, the evidence presented to this Court indicates that scientists generally use confidence intervals or other measures of statistical significance to demonstrate that a detected association is sufficiently greater than the background risk as to be unlikely due to chance alone.

[10] *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 892 (E.D. Ark. 2010); *See also General Elec. Co. v. Joiner*, 522 U.S. 136, 145 (1997)(where an expert's opinion was founded on statistically insignificant findings and other doubtful evidence, the district court did not abuse its discretion in excluding that opinion); *In re Chantix (Varenicline) Prods. Liab. Litig.*, 889 F. Supp. 2d 1272, 1290 (N.D. Al. 2012)(noting that " if an expert places undue emphasis or statistically insignificant evidence, it may indicate that the expert's methods are unreliable.")

[11] Opinion at 8-11.

of the relevant Bradford-Hill criteria.[12] In so doing, the Court rejected Pfizer's argument that the Court could exclude Dr. Bérard's opinion without even reaching her Bradford-Hill analysis, because the Bradford-Hill criteria should only be applied after an association is well established.

The Court notes that Dr. Bérard's failure to point to replicated, statistically significant findings supporting her conclusions about teratogenic effects was one identified methodological flaw, but was by no means the sole basis for its exclusion of Dr. Bérard's testimony. In addition to this methodological issue, the Court found (as discussed above) that the Rothman approach, as applied by Dr. Bérard in this case, did not meet the *Daubert* standard, and the Court also identified other problems with Dr. Bérard's methods, including her failure to test certain critical hypotheses; her failure to reconcile her previously expressed opinion that Zoloft is a "first line" drug for use during pregnancy (which she expressed in publications and presentations as recently as 2012) with the opinion she expressed in this MDL that Zoloft is a teratogen which should be avoided by women who are or may become pregnant; the cherry-picking of studies and data within studies which supported her opinion; her failure to adequately address certain confounding factors; and other "cracks in [her] scientific foundation,"[13] before reaching its evidentiary ruling.

Although the PSC points to the Third Circuit's 1990, pre-*Daubert*, *DeLuca* opinion[14] as support for the proposition that statistical significance *cannot* be used as a threshold criterion for expert reliability, the Third Circuit did not so hold. The Third Circuit noted that plaintiff's proposed expert, faced with a lack of statistically significant findings suggesting an association between maternal use of the medication Bendectin during pregnancy and birth defects, was

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[12] Opinion at 19-24.

[13] *Pritchard v. Dow Agro Sciences*, 430 F. App'x 102, 104 (3d Cir. 2011).

[14] 911 F.2d 941.

"[s]ailing against prevailing scientific breeze" and analyzing the data "using an approach, advocated by Professor Kenneth Rothman . . . that places diminished weight on so-called 'significance testing.'"[15] The Third Circuit did not affirmatively endorse Professor Rothman's approach, but remanded the case to the district court to determine whether this novel approach would satisfy Rule 702. In fact, the Third Circuit stated:

> by directing such an overall evaluation, however, we do not mean to reject at this point Merrell Dow's contention that a showing of a .05 level of statistical significance should be a threshold requirement for any statistical analysis concluding that Bendectin is a teratogen regardless of the presence of other indicial of reliability. That contention will need to be addressed on remand. The root issue it poses is what risk of what type of error the judicial system is willing to tolerate. This is not an easy issue to resolve and one possible resolution is a conclusion that the system should not tolerate any expert opinion rooted in statistical analysis where the results of the underlying studies are not significant at a .05 level.[16]

On remand, the district court did not squarely address this issue. It held a hearing and again ruled to exclude plaintiff's proposed expert, finding that the expert used a novel method of calculating relative risks to reach conclusions different from those reached by the original researchers, cherry-picked data and studies, inaccurately graphically demonstrated confidence intervals, improperly weighed data from the two strongest studies (which found relative risks of 1.1 and .8), and failed to consider bias and confounding factors, among other methodological problems. This ruling was affirmed by the Third Circuit, without a published opinion.[17]

In addition to its erroneous interpretation of the Third Circuit's holding in *DeLuca*, the PSC also fails to demonstrate that, in the 24 years since the *DeLuca* case was decided, the Rothman approach has been more widely accepted by epidemiologists. Accordingly, the Court treated the Rothman approach as novel and applied a flexible test to assess the soundness and

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[15] *Id.* at 946.

[16] *Id.* at 955.

[17] *DeLuca v. Merrell Dow Pharma., Inc.*, 791 F. Supp. 1042 (3d Cir. 1992), *aff'd* 6 F.3d 778 (3d Cir. 1993).

reliability of that methodology, in the context of this MDL. This is precisely what the Third Circuit required in its 1990 *DeLuca* ruling. Although the PSC argues at length that the Court came to the wrong conclusion when it found that the PSC had failed to prove that the Rothman approach, as applied by Dr. Bérard in this case, met the *Daubert* standard for reliability, disagreement with the Court is not a proper basis for reconsideration.

Similarly, the Court's ruling is not inconsistent with Supreme Court's holding in *Matrixx*.[18] Plaintiff asks the Court to infer from *Matrixx* that the Supreme Court would reject the need for replicated, statistically significant findings in assessing the reliability of expert causation opinions by epidemiologists in pharmaceutical injury cases. The Court is not persuaded that this is a correct interpretation of the *Matrixx* decision. *Matrixx* was a securities fraud case, and the issue was whether Matrixx should have disclosed to shareholders and potential shareholders anecdotal reports and lawsuits regarding a possible association between its product, Zicam Cold Remedy, and loss of the sense of smell in some users. That is, the relevant question was whether such reports might have been considered material to reasonable shareholders in making decisions to buy or sell stock in a company. Because it was not a product liability case, the plaintiffs in *Matrixx* did not need to prove that the drug caused the adverse outcome in order to succeed on the merits; instead, they needed to establish that the information regarding the alleged association was material and should have been disclosed. On a motion to dismiss, Matrixx argued that the information was not material and that plaintiffs could not prove scienter, because plaintiffs could not point to any study or report demonstrating a statistically significant association between Zicam and the adverse event. The district court agreed with this argument, and dismissed the case. The appellate court reversed. The Supreme Court affirmed the

[18] *Matrixx Initiatives, Inc. v. Siracusano*, 131 S. Ct. 1309 (2011).

Ninth Circuit, declining to impose a bright-line rule requiring a statistically significant association to plead *materiality* to a shareholder, holding that in some factual circumstances, adverse event information could be material to reasonable investors even in the absence of a statistically significant association, and further noting that a "lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events . . . [as] medical experts rely on other evidence to establish an inference of causation."[19] The Supreme Court further noted that the FDA sometimes requires warnings or takes regulatory action on the basis of evidence that suggests but does not prove causation, and such evidence would also be relevant to shareholders. The Supreme Court therefore held that the complaint stated a claim under securities laws and remanded the case for discovery and further proceedings. Because the facts and procedural posture of the Zoloft MDL are so dissimilar from those presented in *Matrixx*, this Court reviewed but did not rely upon *Matrixx* in reaching its decision regarding Dr. Bérard. However, even accepting the PSC's interpretation of *Matrixx*, the Court's Opinion is consistent with that ruling, as the Court reviewed Dr. Bérard's methodology as a whole, and did not apply a bright-line rule requiring statistically significant findings.

Finally, the PSC argues that the Court's finding regarding the importance of statistical significance in the field of epidemiology is inconsistent with the work of Bradford Hill. The PSC points to a 1965 address by Sir Austin Bradford Hill, which it has not previously presented to the Court, except in opening statements of the *Daubert* hearings.[20] The PSC failed to put forth evidence establishing that Bradford Hill's statement that "I wonder whether the pendulum has not swung too far [in requiring statistical significance before drawing conclusions]" has, in the decades since that 1965 address, altered the importance of statistical significance to scientists in

[19] 131 S. Ct. at 1319.

[20] See April 7, 2014 Tr. at 87-88.

the field of epidemiology. In contrast, the parties did not dispute that Bradford Hill's causation criteria have been widely adopted by scientists.

IV. CONCLUSION

The Court previously found that Dr. Bérard departed from the generally accepted methods and principles of her field in multiple ways, and does not find, on reconsideration, that it committed an error of fact or law or abused its discretion[21] in excluding Dr. Bérard's testimony as unreliable under the *Daubert* standard. Accordingly, the PSC's motion is denied. An appropriate Order follows.

[21] Although abuse of discretion is not the standard of review for a motion for reconsideration, it is the standard of review the Third Circuit will apply if the Court's ruling is appealed. *General Elec. Co. v. Joiner*, 522 U.S. 136, 141-42 (1997).